# Guidance for Industry

## M-4: CTD — Efficacy

## Questions and Answers

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**October 2003**
**ICH**

**Revision 1**

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## M-4: CTD — Efficacy Questions and Answers

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*Contains Nonbinding Recommendations*

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## I. INTRODUCTION

This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the U.S. Food and Drug Administration (FDA). This guidance provides answers to questions that have arisen since the finalization of the harmonized CTD guidance documents in November 2000. This guidance specifically addresses questions related to efficacy. Other question and answer (Q &A) guidances are under development to address general questions as well as questions related to quality and safety. The questions and answers provided here reflect the consensus of the ICH parties.

This guidance is being revised to include additional questions

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was developed within the M4 CTD-Efficacy Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, September 12, 2002. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

## II. BACKGROUND

The guidance for industry issued in November 2000 on preparing the CTD was divided into four separate documents (1) M4: Organization of the CTD, (2) M4: The CTD — Quality, (3) M4: The CTD — Efficacy, and (4) M4: The CTD — Safety. Since implementation of these guidances, a number of questions regarding the various CTD documents have been submitted to the various ICH regions. The ICH has developed a process for responding to questions submitted to the ICH Web site. This guidance addresses questions about the Efficacy document. The other Q & A guidances under development address general questions about the CTD and questions related to the Safety and Quality documents.

## III. QUESTIONS AND ANSWERS

***Q1: Clinical study reports contained in Module 5 are cited in the Clinical Overview and/or the Clinical Summary in Module 2. Each clinical study report may be given a unique short name when cited. Does the method of citing and naming have to be uniform throughout all modules?***

A1: We recommend that each study have a unique short identifier that is used consistently throughout the application. The applicant can select the identifier. The full title of the study is provided in the Tabular Listing of All Clinical Studies (Section 5.2)

***Q2: Definitions/Terminology***

***What is the definition of* Common Adverse Events *as used in the CTD?***

A2: Guidance is provided by ICH E3 Guideline.

***Q3: Section Numbering/Title (in Module 5)***

***In Module 5 of the CTD, is it necessary to have a section number for each clinical study report in a certain section, or is it enough just to mention the title:***

***5.3.5 Report of Efficacy….***
***5.3.5.1 Study Reports….***
***5.3.5.1.1 Placebo Controlled….***
***Study XXX***

A3: See ICH granularity document.

***Q4: How many pages should a Clinical Summary be for an application that contains multiple indications?***

A4: The estimated size of this document is 50-400 pages, assuming one indication. Applications that include multiple indications will be larger, reflecting the submission of multiple efficacy sections.

***Q5: Section "2.7.3.3" Comparisons and Analyses of Results Across Studies***

***The Guideline provides "This section should also cross-reference important evidence from Section 2, such as data that supports the dosage and administration section of the labeling." However, this Guideline also provides a Section, "2.7.3.4. Analysis of Clinical Information Relevant to Recommended Dose." Please specify how to differentiate the two sections "2.7.3.3" and "2.7.3.4".***

A5: Section 2.7.3.3 summarizes the data across all studies that characterize efficacy of the drug; Section 2.7.3.4 provides an integrated summary of the dose-response or blood concentration-response relationships of effectiveness. In both cases, supportive data from Section 2.7.2 can also be incorporated.

***Q6: Overall Extent of Exposure***

***In the Guideline, a table is required to be generated to present the overall extent of drug exposure in all phases of the clinical development. Should the table include "patients alone" or "patients and healthy subjects"?***

A6: That table should refer to all subjects exposed to at least one dose of the drug product. Appropriate subsets of subjects relevant to the proposed indications should also be identified and considered.

***Q7: Summary of Clinical Safety***

***Where should information be described concerning the validity of extrapolation of foreign clinical safety data to a new region?***

A7: Summaries of any bridging studies using clinical endpoints (i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5)) should be included in Section 2.7.3.2. Where appropriate, such information should also be described in the summarization of safety data as related to intrinsic and extrinsic ethnic factors (ICH E5), in Sections 2.7.4.5.1 and 2.7.4.5.2. Finally, some applications might include in Section 5.3.5.3 a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information. Such information should be included in that detailed analysis of bridging.

***Q8: Bioavailability/Bioequivalence Study Data***

***Where should the information on bioequivalence studies for a generic application be included?***

A8: Bioavailability study reports should be included in Module 5 (Clinical documentation), under section 5.3.1 "Reports of Biopharmaceutical Studies". More specifically, reports of comparative Bioavailability/Bioequivalence studies should go under section 5.3.1.2.

***Q9: Tabular Listing of Clinical Studies in Paper CTD***

***In Module 5, 5.2 is denoted as the 'Tabular Listing of all Clinical Studies'. Is this section for a summary listing of all clinical studies in the submission, or it is for the listing of the individual study reports? In other words, should the listings from the appendices of the individual study reports be included here, rather than as an appendix to the CSR, or are these only listings that summarize all studies?***

A9: The tabular listing described in section 5.2 is a listing of all clinical studies in the submission.

An example of such a listing is given in Table 5.1.

***Q10 Integrated Summary of Safety and Effectiveness***

***Does the CTD section on safety in Module 2 replace the section under 21 CFR 314.50(d)(5)(v)-(vi) calling for integrated summary of safety and effectiveness (ISS/ISE)?***

A10: The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDA's guidance *Format and Content of Clinical and Statistical Sections of Application* gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries.

The Clinical Safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (*Structure and Content of Clinical Study Reports*). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis.

If the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, the CTD Module 2 section ***would*** fulfill the need for an ISS/ISE. In some cases, it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5.

Any questions about these matters can be raised with the reviewing division.